

STERILITY IN WOMEN (induction of ovulation)

THESE

présentée à la Faculté de médecine de l'Université de Genève
pour obtenir le grade de docteur en médecine

par

Raad Maulood MUKHLIS

de

BAGHDAD (Irak)

Thèse No 3530

GENEVE

Editions Médecine et Hygiène

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La Faculté de médecine, sur le préavis du professeur Hubert de Watteville, autorise l'impression de la présente thèse, sans prétendre par là émettre d'opinion sur les propositions qui y sont énoncées.

Genève, le 16 septembre 1976

Le doyen :
Marcel Jenny

Thèse No 3530



ACKNOWLEDGEMENT

All my life I will be indebted to Professor Hubert de Watteville, for all that he has taught me, all the help he has given me, and the interest he has always shown in my work. He has been more than a professor to me, he has been a great friend.

TO MY MOTHER

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PREFACE

Since childhood, I have dreamt of becoming a Medical Doctor. Over the years when I have worked so hard, and particularly when I started attending the clinical subjects in medicine, I began to feel drawn towards gynaecology and obstetrics, that was the first reason I took this subject as a profession.

During my first years of practice in Europe and in my own country, (Iraq) I became interested in sterility in women. I discovered that anovulation in women is one of our most difficult problems, yet at the same time one of our most interesting subjects.

I came to Geneva and worked in the Cantonal Hospital, studying and working until I earned my Specialist Diploma. During this time I mentioned to the Authorities in Geneva Medical School that I wished to obtain the degree of Doctor in Medicine, from the same school. After a great deal of discussion we agreed that my theses should be concerning sterility in women, and especially with the subject of ovulation.

ANATOMY

THE HYPOTHALAMUS

The hypothalamus forms the floor of the IIIrd ventricle. It includes, from before backwards, the optic chiasma, the tuber cinereum, the infundibular stalk (leading down to the posterior lobe of the pituitary), the mamillary bodies and the posterior perforated substance. In each of these there is a number of cell masses or nuclei surrounded by a fiber pathway-the medical fore-brain bundle-which runs throughout the length of the hypothalamus and serves to link it with the midbrain posteriorly and the basal fore-brain areas anteriorly. From a functional point of view the hypothalamus is largely concerned with autonomic activity and can be divided into a postero-medial sympathetic area and an antero-lateral area concerned with parasympathetic activity.

THE PITUITARY GLAND (Hypophysis Cerebri)

This is the example of a "two in one" organ of which Nature is so keen, compare the two glandular components of the adrenal cortex and medulla, and the exocrine and endocrine parts of the pancreas and testis. The pituitary comprises a larger anterior and smaller posterior lobe, the latter connected by the hollow infundibulum (pituitary stalk) to the tuber cinereum in the floor of the IIIrd ventricle.

The two lobes are connected by a narrow zone termed pars intermedia. The anterior lobe is extremely cellular and consist of chromophobe, eosinophilic and basophilic cells. The pars intermedia contains large colloid vesicles reminiscent of the thyroid. The posterior lobe is made up of nerve fibres whose cell stations lie in the hypothalamus.

THE OVARY AND ITS DEVELOPMENTS

The ovaries are the female gonads or sex glands and are the homologues of the testis. Each gland is oval in shape, pinkish gray in colour, and during reproductive life its surface is irregular and scarred, due to the presence of large follicles, cysts or corpora lutea and to the effect of shrinkage of the corpora albicantia.

The size of the ovaries varies in different individuals, and is also subject to some variation in the same individual depending on the stage of the sexual cycle. Its length varies from 2.5 to 3.5 cm., and is about 2 cm. broad and 1.5 cm thick.

In nullipara, the ovary lies in a shallow peritoneal fossa on the lateral pelvic wall known as the fossa ovarica of Waldever. Its long axis lies in the vertical plain, so that it has an upper and a lower pole, an anterior and a posterior border, and a medial and a lateral surface.

The ovary is attached to the posterior layer of the broad ligament by the mesovarium, to the lateral pelvic wall by the infundibulo-pelvic fold, to the uterus by the ovarian ligament. The position of the ovary is therefore likely to be influenced by the movement of the broad ligament and the uterus under normal circumstances.

Blood supply to the Ovary is from the long, slender ovarian artery, a branch of the abdominal aorta.

Venous Drainage is into a pampiniform venous plexus from which the ovarian vein emerges. This opens on the right side into the left renal vein at a right angle.

Lymphatic Drainage is into the lateral aortic nodes near the kidney, since the ovary is developed in that region.

All blood vessels, nerves and lymphatics enter the infundibulo-pelvic fold, broad ligament and mesovarium to reach the hilum of the ovary.

DEVELOPMENT OF THE OVARY

Genetically, the sex of the individual is determined at the time of fertilization, but it is not until the embryo has reached the 17 mm. stage that it is possible to identify the gonad as either a testis or an ovary.

The ovary is developed from the Genital Ridge which lies between the root of the mesentery and the Wolffian ridge on the posterior wall of the coelomic cavity.

The genital ridge lies on the cranial aspect of the developing suprarenal cortex, and this fact provides an anatomical basis for the hormonal interrelation between the suprarenal cortex and the gonads.

This ridge bulges into the coelomic cavity and is formed by a proliferation of the cells of the coelomic epithelium. The surface epithelium, which is a modified form of peritoneum, is called the germinal epithelium. From the surface layer a number of cellular cords containing the future ova migrate deeply into the underlying mesoderm. These cells are the precursors of the Graafian follicles. They are not isolated from the germinal epithelium by the tunica albuginea during the foetal life as are the sex cells in the male, indeed, this is the earliest distinguishing feature between an ovary and a testis.

A rete ovarii is formed, similar to the rete testis, by an invasion of the germinal cells into the mesovarium. The later become canalized and may join with the mesonephric tubules as in the male, and in any case they remain rudimentary.

Some authorities regard the rete as being mesonaphric in origin. This embryonic remenant is of importance only because it may give rise to cysts, which because of their close proximity to the tubal fimbriae, are called fimbrial cysts.

The ovary is developed between the tenth and twelfth thoracic segments on the posterior abdominal wall near the kidney. This accounts for its long attenuated blood supply, its venous drainage, its nerve supply from a plexus adjacent to its origin, and also its lymphatic drainage into nodes lying adjacent to the renal veins.

HISTOLOGY OF THE OVARY

The ovary, apart from being the site of the formation of egg cells, is an endocrine gland in which at least two, if not more, important hormones are manufactured and sent into circulation. The one is called the follicular hormone (oestrogen) because evidence points to it being formed by the cells of the 'eggfollicles', the other, the corpus luteum hormone (progesterone), is linked up with the differentiation of certain cells into so called lutein cells.

The histological picture of the ovary differs markedly according to age, to the state of sexual activity and also the stage of the sexual cycle. The formation of a ripe ovum is accompanied by pronounced histological processes.

The ovary is generally divided into a cortical zone and a medulla. The medulla contains numerous blood vessels in particular coiled arteries, lymphatics and nerves embedded in fibrous tissue, and all these structures are continuous at the hilum and those present in the mesovarium.

The Cortical Zone contains, besides the stroma, the so-called 'egg-follicles' and depending on age, those bodies (corpora lutea, corpora albicantia, etc.), which form subsequent to the discharge or degeneration of an ovum. Generally speaking, the smallest immature follicles are to be found at the periphery of the cortex, the more advanced follicles nearer the medulla, and the large mature follicles occupying the whole width of the cortex extending from near the medulla to the surface of the organ.

The ovary is covered by a low columnar epithelium, the so-called germinal epithelium, which joins the flat serosal cells of the peritoneum at the mesovarium. This epithelium, which is easily detached on handling the organ, is nevertheless present even after the climacteric, although it may often be found only in patches. Here and there it is invaginated and in this way covers the irregular surface of the organ, or may even penetrate the underlying stroma by tubular formations. Sometimes its cells are cubical, or even flat, especially when overlying large growing structures such as a maturing follicle or a corpus luteum.

Beneath the germinal epithelium, there, develops with advancing age a connective tissue layer of increasing density called the tunica albuginea containing collagenous fibres.

These are almost absent in the rest of the cortical stroma, which is peculiar in that, besides blood vessels, lymphatics and nerves, it shows an abundance of short and long spindle - shaped nuclei. The cell bodies to which these nuclei belong are difficult to discern in ordinary sections. Most of them, if not all, are probably mesenchymal cells. This richly nucleated stroma is very characteristic of

the human ovary, is established long before puberty, and remains fairly constant in its nuclear density up to old age.

GROWTH AND MATURATION OF EGG FOLLICLES

In the growth and ripening of an egg follicle four main processes are involved :

- (1) Increase in size and maturation of the ovum.
- (2) differentiation and proliferation of the follicle epithelium.
- (3) formation of a fluid, the liquor folliculi.
- (4) formation of a special connective tissue covering from the ovarian stroma, the theca folliculi.

(1) Growth of the Ovum.

This involves the cytoplasm as well as the nucleus, but not in equal proportion, the increase of the former being absolutely and relatively greater. Substances are accumulated in the cytoplasm (now called vitellus) which are necessary-in case of fertilization-for the first developmental stages of the ovum prior to its nidation in the uterus.

The spherical nucleus becomes more and more vesicular with a much thinned-out and brokenup chromatin network , it gradually occupies an eccentric position in the vitellus and is now known as the germinal vesicle. It may contain one or more acidophil nucleoli, the most prominent of which is referred to as the germinal spot. The full-grown living human ovum is very transparent with a finely granular and almost colourless cytoplasm. The ovum is enclosed in a homogeneous hyaline membrane, the zona pellucida. This usually fits tightly around the cytoplasm of

the ovum. If it does not do so or if the cytoplasm shrinks away from the zona, then a space becomes visible called the 'perivitelline space'. It is into this space that the polar bodies are later extruded. The ovum reaches its final size of about 100μ to 120μ diameter (zona pellucida excluded) long before the follicle is mature.

It is worthy of note that the ovum itself is not completely mature on leaving the ovary. Only the first polar body (following the first maturation division) is usually extruded from the ovum when still within the follicle ; the second maturation division of the oocyte seems to begin as in most mammals, just prior to the rupture of the follicle , it is not completed unless simination of the ovum takes place. This usually occurs in the infundibulum of the uterine tube ; and only then and there, the second polar body is formed. Observations on this point in the human are, of course, still scanty.

(2-3) Growth of Follicle and Formation of Liquor

The follicular epithelial cells (f. e. c.) originally flat in the primordial follicle acquire a definite basement membrane, multiply mitotically, become cubical or columnar, and surround the growing ovum (whose nutrition they probably serve) as a dense layer. At this time the zona pellucida is forming, and the current view to ascribe its formation to the activity of the f. e. c. rather than to that of the ovum. In support of this idea thin cytoplasmic processes of the f. e. c. have been described as passing through the zona pellucida conferring on it sometimes a peculiar radial striation. This is confirmed by electron microscopy. By continued mitotic activity and movement the f. e. c. soon form several layers around the ovum.

Except for the outer-most layers, and those surrounding the zona, they lose their columnar shape and tend to become polygonal or stellate with small, mostly round nuclei. Then at one or several places a split occurs between these layers, and into it a serous albuminous fluid, the liquor folliculi, is secreted in ever increasing quantity. The liquor is rich in oestrogen. The fluid areas formed in different parts of the follicle coalesce, and gradually a single large fluid-filled cavity (antrum) is formed which occupies most of the space of the follicle, now called 'Graafian follicle'. The cavity is surrounded by several layers of f.e.c. which at one point contains the ovum. This region usually projects into the cavity-sometimes in the form of a peninsula-and is known as the egg-bearing hill. Its position in relation to the surface of the ovary varies greatly.

The remaining f.e.c. which merely line the liquor-filled cavity are summarily known as the membrana granulosa, probably because these small cells, when viewed with a low magnification, look somewhat like granules. All the f.e.c. are often referred to as granulosa cells. The cells which invest the zona pellucida are called the corona radiata if the radial arrangement is well developed.

Finally, mention should be made of round homogeneous structures, each somewhat the size of an ovum, which form between the granulosa cells. They are known as the Call-Exner bodies, but their significance is not understood.

(4) The Connective tissue covering.

The stroma cells surrounding the follicle, concomitantly, with the above growth processes also proliferate mitotically and form a covering of concentric layers, the theca folli-

culi. A rich capillary network develops in the more internal layers (theca interna) which currently is thought to be the site of oestrogen production, whereas the outer layers are more fibrous (theca externa). When the follicle approaches maturity the fibroblastic cells of the theca interna hypertrophy and become more epithelioid with a granular lipoid-containing cytoplasm and a small spherical nucleus. They are surrounded individually by reticular fibres. The cells may later play some part in the formation of the corpus luteum and have, therefore, been called theca-lutein cells or paralutein cells.

They might well be responsible for the first elaboration of progesterone prior to ovulation, for the changeover in the hormonal follicular function from oestrogen production to that of oestrogen and progesterone is not abrupt but gradual.

In this way then, the Graafian follicle grows to a size of about 10 to 15 mm. diameter and gradually reaches the surface of the ovary. The initial even growth of the follicle is, prior to rupture, suddenly speeded up. At this time a secondary liquor—more fluid than the first—is said to be formed and the cumulus becomes detached from the wall so that the ovum with zona pellucida and adherent follicular epithelial cells comes to float freely in the liquor. An earlier idea that the whole epithelial part of the follicle rotates so as to bring the egg-bearing cumulus near to the future rupture point has thus not been substantiated.

The actual rupture of the follicle, aided by the rise in intrafollicular pressure, is not an explosive process but a gradual opening in which necrobiotic changes in the overlying tissue are involved. The ovum with its zona pellucida and attached follicular epithelial cells is then discharged (ovulation) into the peritoneal cavity.

Ovulation occurs about midway between menstrual periods or, more precisely, about fourteen days before the onset of menstruation.

Corpus Luteum

As the result of the collapse of the follicle - following ovulation - a structure remains with a richly pleated wall, somewhat yellow in colour. This marks the beginning of the development of the so-called corpus luteum. The cavity is still lined by several layers of granulosa cells, which tend to form vertical rows towards the centre, it may be empty to begin with or filled with a clotted mass (tertiary liquor) which also plugs the rupture point.

In case of fertilization of the ovum and subsequent nidation, the corpus luteum will continue to enlarge, become rounder and reach dimensions (2 to 3 cm. diameter) beyond that of the Graafian follicle from which it developed.

If, as in the majority of cases, fertilization does not take place, the corpus luteum is spoken of as a corpus luteum of menstruation.

Follicle Atresia

The majority of egg-follicles degenerates sooner or later. This may happen at any stage in their development. Because they never open, these follicles are spoken of as being atretic. The ovum is often the first to show signs of degeneration.

PHYSIOLOGY

OVULATION AND OVARIAN CYCLE

At the time of puberty the female begins to undergo regular monthly cycles. These cycles, known as sexual cycles, are controlled by the hypothalamus. Releasing factors produced by the nerve cells of the hypothalamus act on the cells of the anterior pituitary gland, which in turn secrete the gonadotropins. These hormones, the folliclestimulating hormone (FSH) and luteinizing hormone (LH) stimulate and control the cyclic changes in the ovary.

At the beginning of each ovarian cycle a number of primordial follicles begins to grow under influence of the follicle-stimulating hormone. Only one of these follicles, however, reaches full maturity and only one oocyte is discharged, the others degenerate and become atretic.

In the next cycle another group of follicles begin to grow and again only one reaches maturity. Consequently, the majority of follicles degenerate without even reaching full maturity. When a follicle becomes atretic, the oocyte and surrounding follicular cells degenerate and are replaced by connective tissue, thus forming a corpus atreticum. During the follicle growth phase large numbers of follicle and theca cells are formed. These cells produce estrogens which stimulate the pituitary gland to secrete luteinizing hormone. This hormone is used to induce the shedding of the oocyte, known as ovulation.

In the days immediately preceding ovulation, the Graafian follicle increases rapidly in size under influence of follicle-stimulating and luteinizing hormones and expands to a diameter of 15 mm.

The surface of the ovary then begins to bulge locally and at the apex an avascular spot appears, the so-called stigma. As a result of local weakening of the ovarian surface, follicular fluid oozes through the stigma, which gradually opens. Subsequently, when more fluid escapes, the tension in the follicle is released and the oocyte together with the surrounding cumulus oophorus cells break free and float out of the ovary. At the moment that the oocyte with its cumulus oophorus cells is discharged from the ovary - (ovulation) - the oocyte begins its second meiotic division.

The periodic shedding of an oocyte and the regular maturation of a group of primordial follicles constitute the cyclic changes in the ovary, referred to as the ovarian cycle. Ovulation takes place once in a cycle, approximately 14 days $\pm$ 1 day before the beginning of the following menstrual bleeding.

Although the time between ovulation and the succeeding menstrual bleeding is constant, the time between ovulation and the preceding menstruation is highly variable and depends on the length of time the follicle needs to mature.

When ovulation occurs, the follicular cells remaining in the wall of the ruptured follicle are vascularized by surrounding vessels and become polyhedral. Under influence of the luteinizing hormone the cells develop a yellowish pigment and change into the luteal cells. These cells form the corpus luteum and secrete progesterone. This hormone, together with the estrogenic hormones produced by the theca cells and the surrounding ovarian tissue, cause the uterine mucosa to enter the pregestational or secretory stage in preparation for implantation of the embryo.

If fertilization fails to occur, the corpus luteum reaches maximum development about nine days after ovulation. It can easily be recognised as a yellowish projection on the surface of the ovary. Subsequently, the corpus luteum decreases in size through degeneration of the luteal cells and forms a mass of fibrotic scar tissue, known as the corpus albicans. Simultaneously the progesterone production decreases, thus precipitating the menstrual bleeding.

THE OVARIAN FUNCTION CONTROL

The release of gonadotrophins is controlled by two hypothalamic factors, the luteinizing hormone release factor (LHRF) and follicle stimulating hormone release factor (FSHRF).

(LHRF) produced in two areas in the hypothalamus and after stored in the median eminence it passes to the anterior lobe of the pituitary through the hypothalamo - pituitary portal circulation.

LHRF if administered to intact animal will stimulate the release of LH from the pituitary and may produce ovulation.

The control of the above phenomena is managed by long and short, negative and positive feedback mechanism.

In the long - ve feedback mechanism the oestrogen acts on the hypothalamus to reduce its stores of LHRF.

In the + ve feedback the oestrogen will decrease LH stores and increase plasma LH.

In the short - ve feedback, the implantation of LH into the hypothalamus will decrease the store of LH in the pituitary.

FSHRF is produced in one area of the hypothalamus and stores in the median eminence.

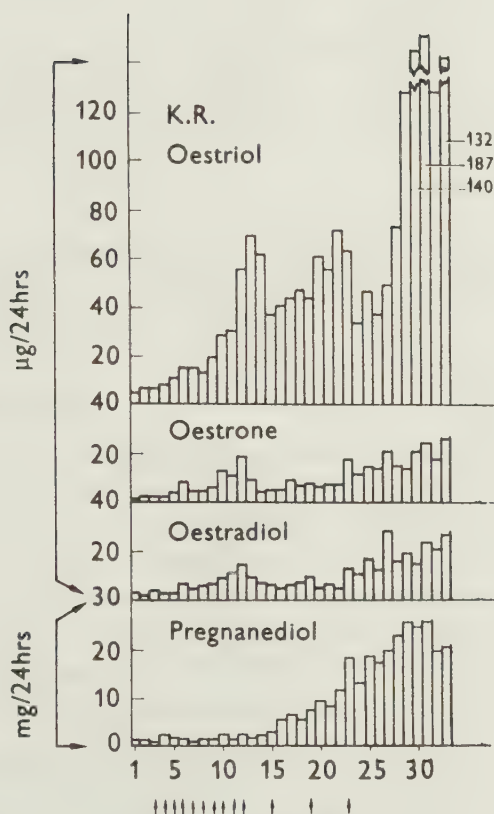
FSHRF if administered to intact animal will increase the level of FSH in the plasma and will decrease the pituitary FSH, and if administered to anovulatory women it will induce ovulation.

Giving oestrogen reduce the pituitary FSH while oestradiol reduce FSHRF in the hypothalamus progesterone inhibit both FSH and FSHRF.

Exogenous FSH produce a decrease in FSH and FSH - RF.

The human gonadotrophins are two : -

1. FSH is capable of producing follicular Maturation, but it can not induce ovulation or initiating ovarian steroidogenesis and for this purpose LH is needed.
2. LH is responsible for luteinization and the effect of promoted steroidogenesis on the genital tract but also FSH is important here. LH encourages steroidogenesis after exposure to FSH and these are of three groups.



Days 3-9 -75 i.u. F.S.H. (Pergonal)

Days 10-11 -150 i.u. F.S.H. (Pergonal)

Day 12 -75 i.u. F.S.H. (Pergonal) + 2,000 units H.C.G.

Days 15,19 and 23 -500 units H.C.G.

Fig. No. 1

Urinary steroid excretion during
a conceptual cycle.

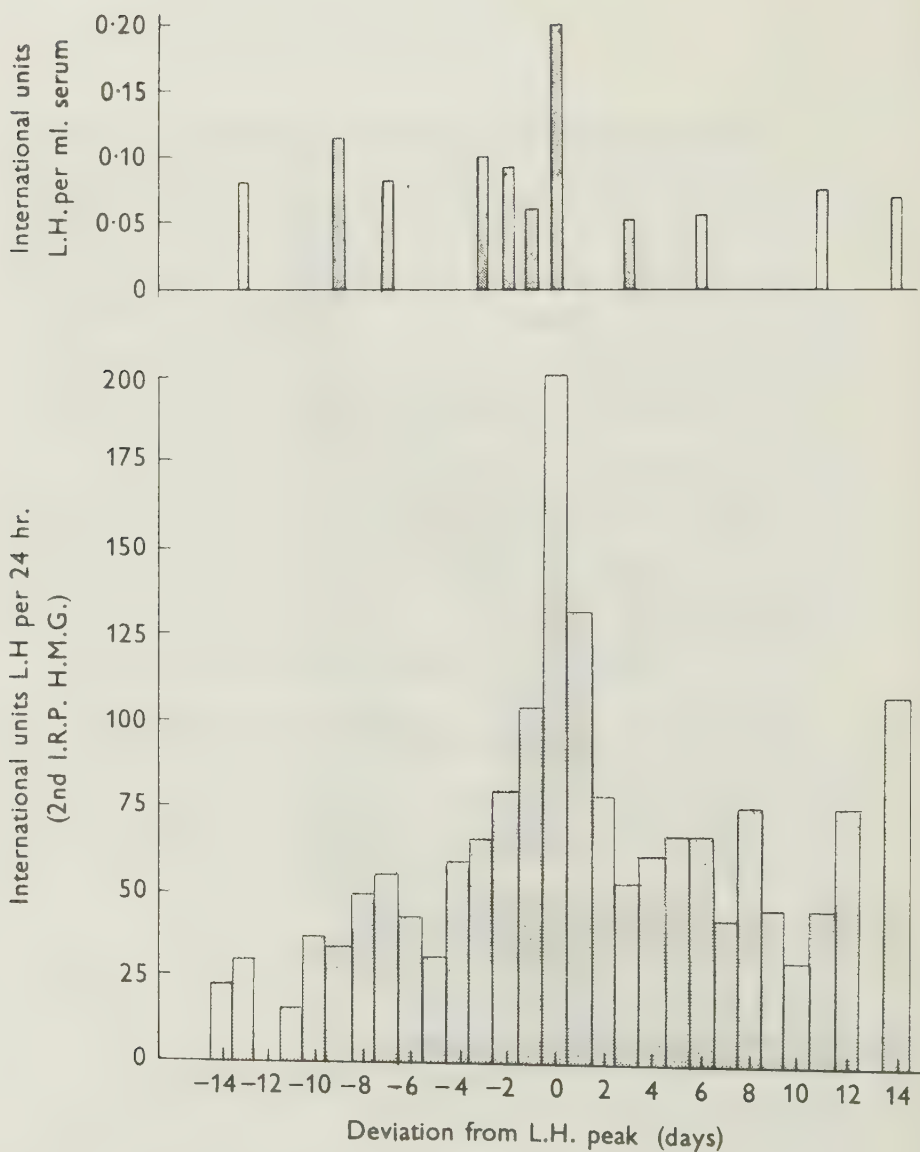


Fig. No. 2

Urinary and serum levels of luteinizing hormone during the normal menstrual cycle.

- (a) The stroma, produce andostenedion testosterone and some progesterone and oestrogen.
- (b) The follicle, produce oestradiol and little progesterone and androgenes.
- (c) The corpusluteum, produce progesterone and some oestradiol.

The hormones produced by the ovaries depends on the stimulation of the pituitary gonadotrophins to the ovarian follicli and corpus luteum

Oestrogens

There are several oestrogens the main types are Oestradiol, Oestron and Oestriol, but the oestrogen secreated by the ovary is Oestradiol which is then partly converted to less active oestron and oestriol and also combined with glucaronic acid before excretion in the urine as 10 % of the whole ovarian output and the rest are fixed by the endometrium or inactivated by the liver. The maximum urinary output is about 100 µg/ 24 hours.

Progesterone

It is the precursor in the body of corticosteroids, androgines and oestrogenes. It is found in the blood in low constant level.

It is excreted in the urine in the form of pregnanediol and the maximum output of pregnanediol is about 5 mg/ 24 hours. (In the third week of the cycle).

Androgens

Some androgens are secreated in the body and then excreted in the urine. It has only a small physiological role in the woman which is of no importance.

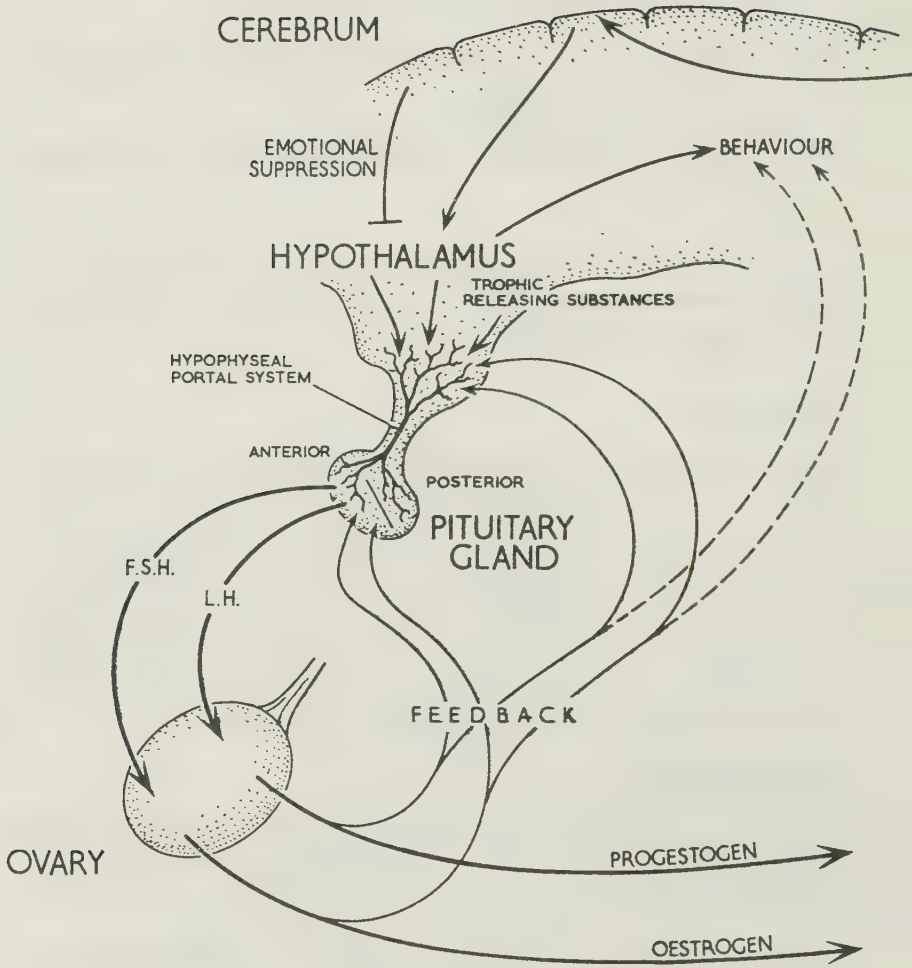


Fig. No. 3

Diagram showing hypothalamus-pituitary-ovarian-uterine relationship.

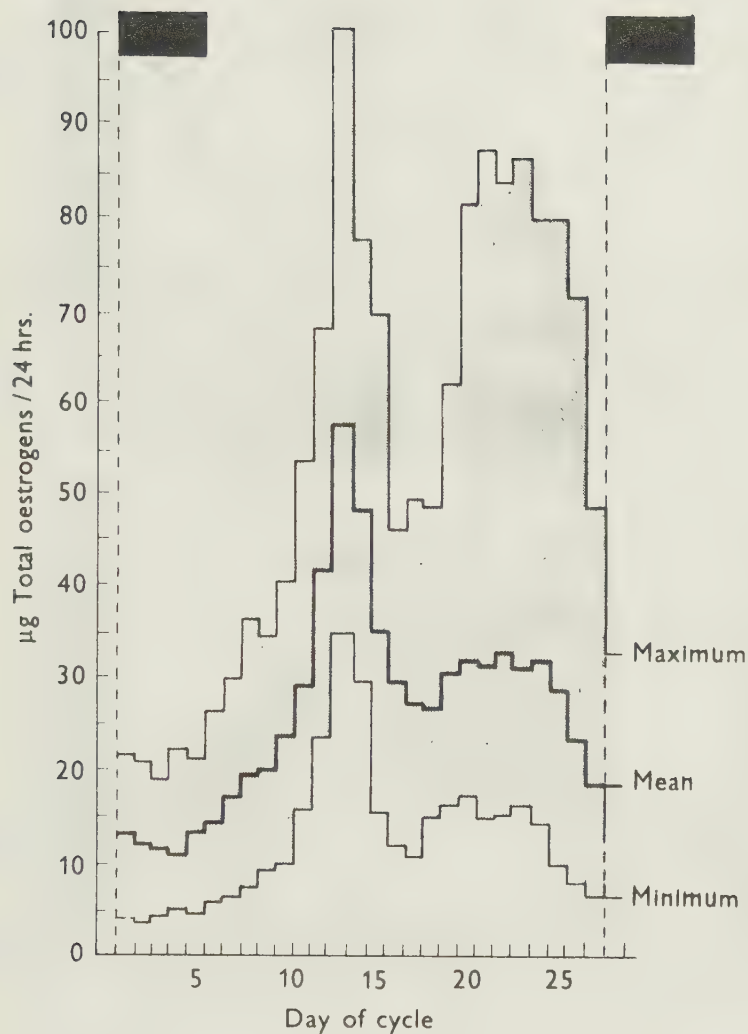


Fig. No. 4 Mean and range of urinary excretion of total oestrogens during the normal menstrual cycle.

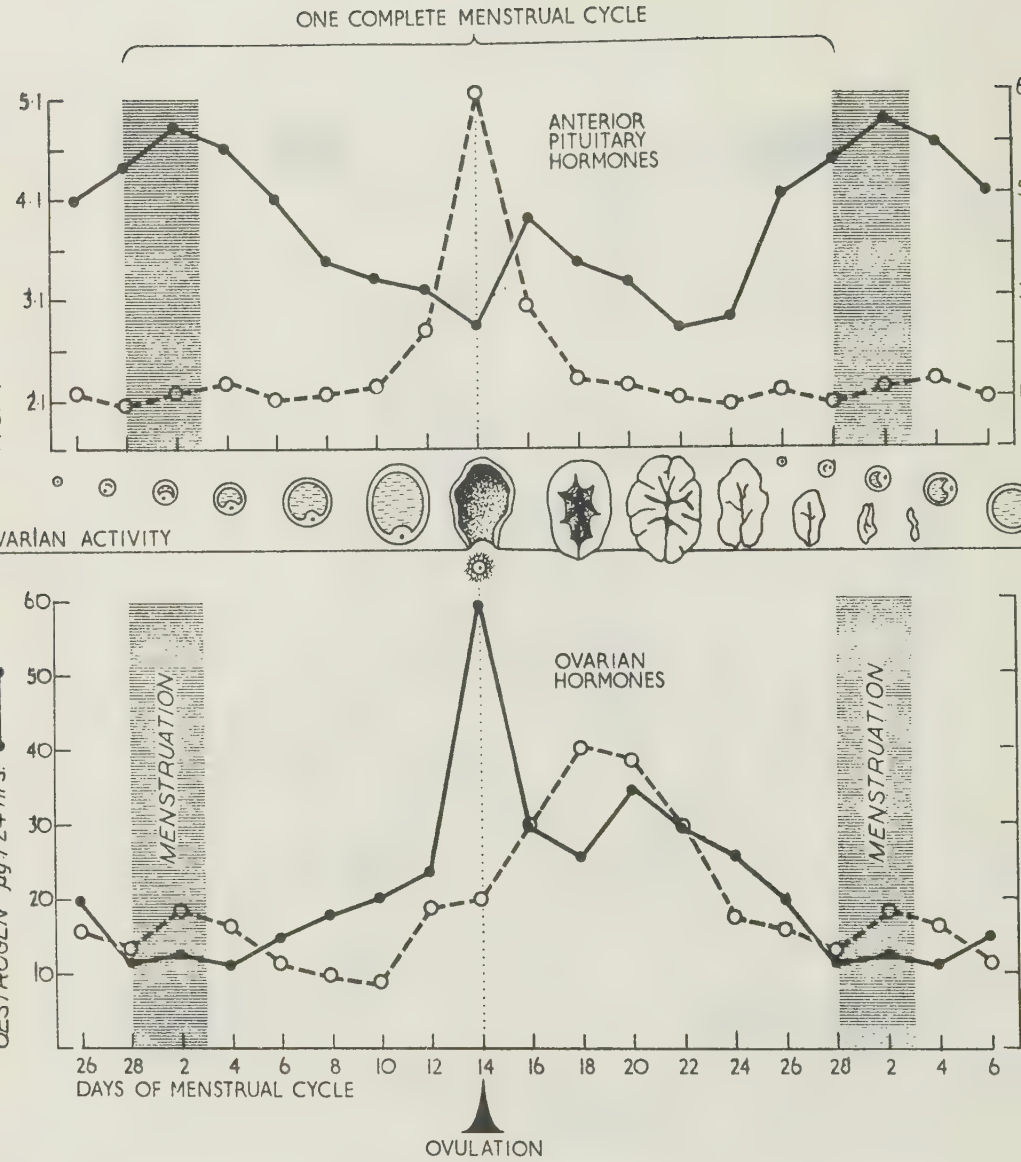


Fig. No. 5

Hormone levels in the normal cycle considering variations are compatible, however with normal menstrual functions.

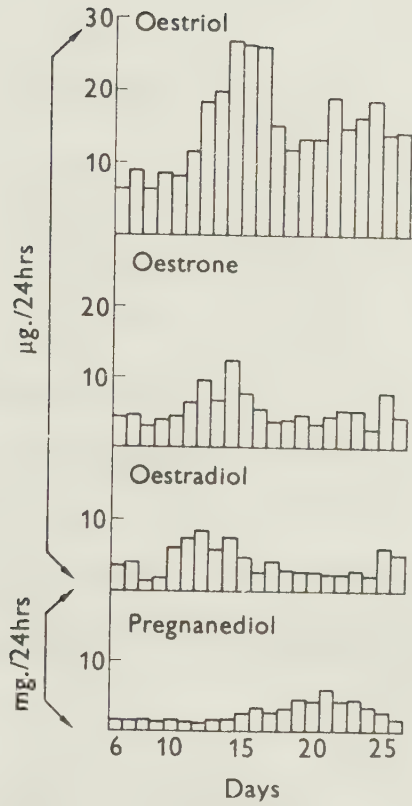


Fig. No. 6

Excretion of oestrogens and pregnanediol during the normal menstrual cycle.

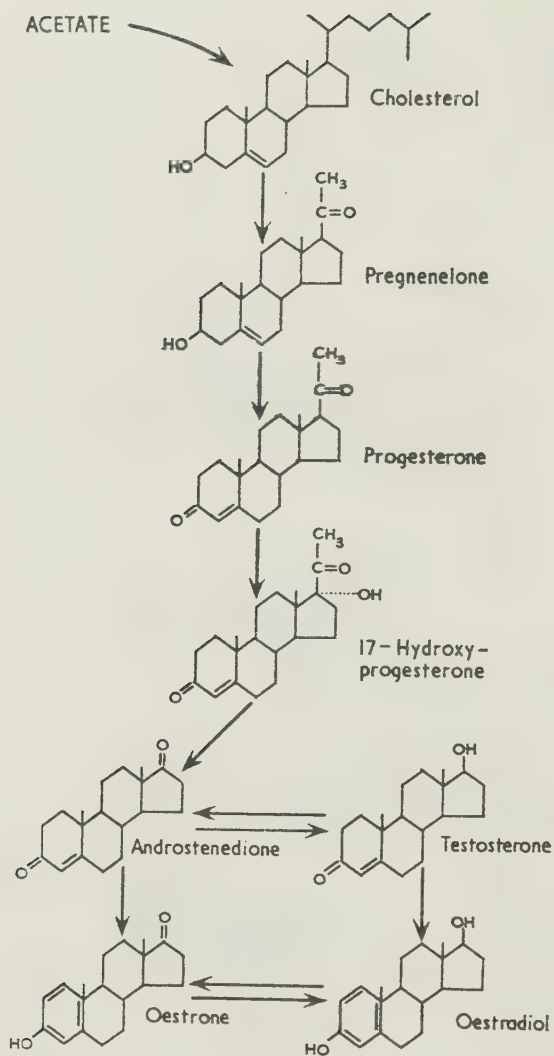


Fig. No. 7 Pathways of sex hormone synthesis.

AMENORRHOEA

Absence of menstrual periods.

It might be false in character when the menstruation occurs but the passage is obstructed, this condition is called cryptomenorrhoea.

Or it might be True amenorrhoea in which there is a suppression of the menstrual function.

The cause of true amenorrhoea might be physiological as for example amenorrhoea before puberty or in cases of pregnancy lactation or menopause.

Or it might be Pathological in nature in which we have to investigate and treat.

Pathological Amenorrhoea

Amenorrhoea itself is a symptom but not a disease. It has many aetiological factors and for clinical purposes it divides into primary and secondary types.

Menstration depends on the right function of the hypothalamus and pituitary, ovary and uterus, any brake or weakening in one or more of them might produce amenorrhoea.

Etiology

(1) Primary Amenorrhoea

I. Chromosomal factor.

eg. Turner syndrome
mixed gonadal dysgenesis

2. Gonadal Factor.

- eg. True hermaphrodite
True gonadal agenesis
Virilisms
- 3. End Organ Resistance
 - eg. Testicular feminization
Cryptorchid hypospadiac Male intersex.
- 4. Hypothalamus Pituitary Disorders
 - eg. Pan hypopituitarism
asexual ateliotic dwarfism
lawrence - moon - beidl syndrome
olfacto genital syndrome
Hypogonadotrophic eunuchoidism
Pre-pubertal polycystic ovaries
- 5. Adrenal Hyperplasia
- 6. Gynaetresia
 - eg. Congenital absence of uterus and vagina
cryptomenorrhoea
- 7. Delayed Menarche
- (2) Secondary Amenorrhoea
 - 1. Uterine factors
 - eg. atrophies after X-rays or radium
T.B' endometritis
Asherman's syndrome
 - 2. Ovarian Causes

- eg. Abilation or radiation
Stein-Leventhal syndrom
Follicular cysts
Granulosa-theca cells tumours
Arrhenoblastoma
Ill health and infection
- 3. Pituitary Disorders
- eg. Hypopanpituitarism (simmon's disease)
Pituitary neoplasm
- 4. Hypothalamic disorders
- eg. emotional factors act on the hypothalamus
Organic lesions (Fröhlich and chiari -
Frommel syndromes)
Ill health and starvation
- 5. Other Endocrine Causes
- eg. Hyperthyriodism
diabetes
Adrenal tumour or hyperplasia
- 6. Iatrogenic Causes
- eg. Oral Contaception
Phenothaizines and some hypotensive drugs.

INVESTIGATIONS FOR OVULATION

It is very important to notice that menstruation does not necessarily mean ovulation as it is very often found that patients with normal cycle do not ovulate. It is unnecessary to start investigations on a patient with amenorrhoea unless the patient wishes to become pregnant, or without a full investigation of her partner.

To start an investigation of a patient who does not ovulate, we should begin with the most usual problems and work our way upward.

The medical history and the general physical examinations are very essential in the investigations as during which we can notice the physiological condition of the patient, the weight changes, the presence of hair growth changes as in the hirsutism, also the presence of galactorrhoea is important if the patient developed the condition of amenorrhoea after childbirth. The physical examination can determine the presence of Cushing's syndrome, or Addison's disease, also some signs and symptoms might indicate a polycystic ovaries.

X-Ray of the chest, the skull and pituitary fossa are important to diagnose pulmonary TB. or pituitary lesions.

I in case of Imperforate hymen the patient might complain of vaginal atresia, absent uterus or ambiguous sex, in these cases special investigations are needed.

- a) Barrbodies
- b) Karyotype

- II In case of Polycystic Ovarian syndrome the investigations are : -
- a) Raised urinary pregnanetriolone
 - b) Laparoscopy
- III In case of the presence of normal uterus, or small, the investigations are : -
- a) Basal body temperature in which we can determine the occurrence of ovulation, because the hormone progesterone is thermogenic so the temperature will rise after ovulation by 0.2 to 0.5°C over the pre-ovulation period.
 - b) Vaginal cytology. This is done by taking a smear from the lateral wall of the vagina and to note the cyclic changes which occur during the cycle and also to determine the oestrogen - progesterone ratio.
 - c) Mucus of the cervix. This is done to obtain the Ferning Phenomenon which occurs before ovulation due to the action of oestrogen and disappears after ovulation due to the action of progesterone.
 - d) Endometrial Biopsy, in this kind of investigation we can obtain good information about the changes in the Endometrium, the Corpus Luteum or any disorders in the endometrial tissue.
 - e) Direct Observations. This is done by Laparotomy or Laparoscopy in which we can see the corpus luteum formed after a recent ovulation, or we might observe the ruptured follicle on the day of ovulation, also ovarian biopsy can be obtained through this way for further investigations.

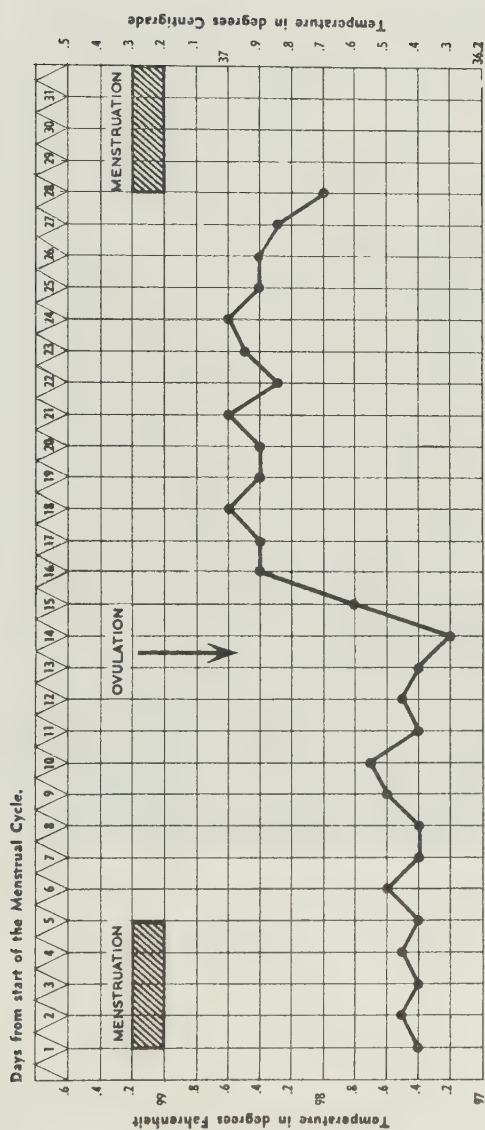


Fig. No. 8 A biphasic temperature chart indicating that ovulation was presumed to have occurred on day 14 of the cycle.

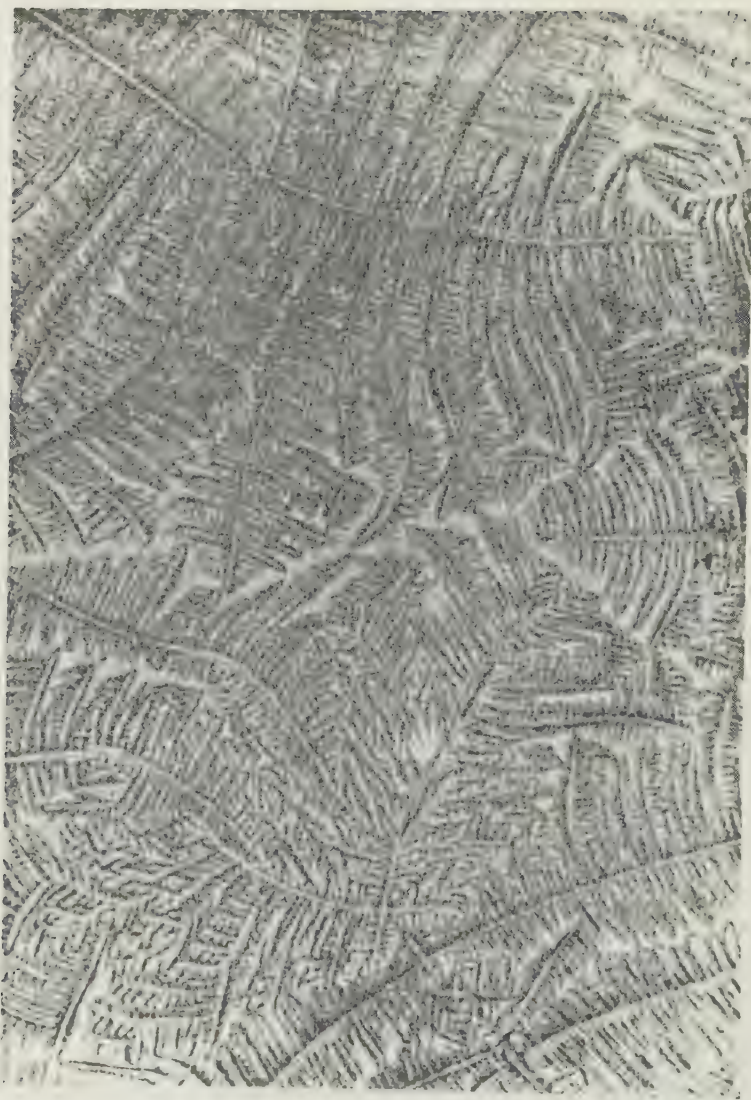


Fig. No. 9

Cervical mucus-ferning.

f) Hormonal Essay.

In this respect the total oestrogens level in urine is the most easily indicative method and the observation will divide into two aspects.

- i) The level is more than $10\mu\text{g}/24$ hours, in this case estimation of 17Oxy and hydroxy steroids is indicated. If the level is raised the cause most probably is Adrenal in origin. If the level is normal the cause might be Idiopathic anovulation or psychogenic.
- ii) If the level is less than $10\mu\text{g}$ per 24 hours, Gonadotrophin stimulation test is essential and in this test 5,000 units of pregnant mares serum (PMS) or 75 - 225 international unit human menopausal Gonadotrophin (HMG) daily for three doses, and then estimation of the total oestrogens of 24 hours on the 7th day has to be performed. If the level is less than $5\mu\text{g}$ the cause most probably is ovarian failure, if the level is between 5 to $80\mu\text{g}$ the cause is most probably psychogenic in origin and if the level is 100 up the cause might be Pituitary Failure.

Progesterone assay in the blood is very important nowadays and the assay of FSH and LH might be of great benefit as well, also the LH/FSH releasing factors, but these tests are only practical in special centres with highly developed laboratory services. Recently Prolactin level in the blood has been proved to be of some help in this subject and a long study is taking place on it, a high level of prolactin in the blood may produce anovulation.

INDUCTION OF OVULATION

To start the treatment of anovulation in an infertile patient we should start a very thorough investigations so as to know exactly the cause or causes for the problem. Sometimes we will find that the cause is outside the reproductive axis, eg. general diseases like diabetes, T.B., thyroid, dysfunction, or anorexia nervosa, in these cases the treatment should be directed towards curing them as most probably they are the causes of anovulation.

Sometimes the cause may be corrected by surgery, as in Cushing's Syndrome when adrenalectomy is indicated or in cases of virilizing tumour of the ovary when the excision of the tumour is indicated as well as in the presence of functional tumours of the ovary.

Sometimes the treatment can be surgically or medically, and the choice of either one of them depends on the patient's situation, and on the doctor's ideas.

Induction of Ovulation is one of the most complicated subjects at present. Information on this subjects grows daily. New theories and ideas are continuously being suggested, with the result it is now difficult to choose a method of treatment as every theory has its advocates and arguments. Personally after a reasonable time of practice in Geneva and after studying and revising a good number of books and articles written on this subject, I find I am more inclined to trust the methods followed by some authorities for the last ten years, so as to be familiar with, and prepared for, any side-effects which may result after treatment.

Of course, before starting treatment, the Doctor must consider carefully before using any treatment that could produce severe side-effects, (or any side-effects) on the patient afterwards.

TREATMENT BY CORTICOSTEROIDS

Regular treatment with small doses of Cortisone usually indicated in cases of Adrenogenital syndrome and this will correct the ovarian function. The same treatment is also indicated in Addison's disease (Adrenal cortical failure), in these cases the urinary 17/oxosteroids has to be between 6-10 mg. per 24 hours. The dose usually recommended for treatment is between 5-10 mg/day of prednisone.

TREATMENT BY OESTROGENS

Some Authorities believe that ovulation can be induced by producing a rebound release of gonadotrophins. This is done by giving Stilboestrol, dosage 1 mg. T D S orally, sometimes progesterone may be combined with oestrogen to decrease its side effects.

TREATMENT BY CLOMIPHENE CITRATE

1 - (P - (B - diethylaminoethoxy) - phenyl) - 1,
2 - diphenyl - 2 chloroethy citrate.

The usual presentation comprises a mixture of the cis - and trans - isomers of Clomiphene citrate and the former is more active between them, but the pharmacological preparation is mixed and commercially called clomid. The root of administration is oral where it is rapidly absorbed and metabolized in the liver.

Its action mainly as anti oestrogens as an inhibitory factor on the hypothalamo - pituitary axis and this will produce Gonadotrophins release and also it may encourage the ovaries to be more sensitive to gonadotrophins, but more or less its action is not very clear.

After administration of clomiphene a rise in the excretion of FSH will occur and this will be followed by a rise in the excretion of oestrogene and LH.

Clomiphene is a strong drug and should be given with great care as it is extremely contra-indicated in the case of impaired liver function or ovarian cyst or tumour. Clomiphene is also of no benefit in cases of ovarian failure, panhypopituitarism and hypogonadotropic eunuchoidism.

Clomiphene is strongly recommended in cases of :

- 1) endometrial hyperplasia associated with infertility.
- 2) polycystic ovaries
- 3) anovulation and cases of scattered ovulation during the patients life.

The side-effects that may appear after treatment with clomiphene are : -

- 1) Hyperstimulation with ovarian enlargement and lower abdominal pain
- 2) heat flushes
- 3) Misty vision
- 4) Hair loss
- 5) Galactorrhoea
- 6) Multiple pregnancy

Dosage

Clomiphene has to be used after careful investigation, it can be used alone or in a combination of Human Chorionic gonadotrophins or human menopausal gonadotrophins, in cases where clomiphene alone does not give good results. Again, after a reasonable personal experience and after I had studied and revised the different methods of treatment I am more inclined to agree with the following treatment : -

In cases of secondary amenorrhoea ;
50 mg/day for five days.

If after 30 days the patient does not begin to menstruate, or become pregnant, 100 mg/day for five days.

If again after 30 days the patient does not begin to menstruate or become pregnant, 150 mg/day for five days, if there is no response, 150 mg/day for 5 days.

If ovulation occurs during the time of these courses treatment continues with the same dose every cycle, starting on the fifth day until the patient becomes pregnant, or starts bleeding on account of the treatment.

The patient has to be checked before each course of treatment, and if any ovarian enlargement is noticed, the treatment must be stopped until the ovary returns to normal size.

Clomiphene is also used for treatment of anovulatory cycles and should be started on the fifth day of the cycle.

Treatment must be stopped in all cases if there is no response after the third course, and human gonadotrophin has to be used instead.

The response to clomiphene treatment differs from patient to patient, but usually ovulation occurs between 7-12 days after starting the course of treatment.

TREATMENT WITH GONADOTROPHINS

1. Human chorionic Gonadotrophin (HCG) its first action is Luteinization.
2. Human pituitary Gonadotrophin (HPG) its action is to help and produce follicular maturation. If given together with HCG ovulation might occur.
3. Human menopausal Gonadotrophin (HMG) its action is very good in producing ovulation.

Gonadotrophins have many side-effects, they can cause severe hyperstimulation which could kill the patient. Therefore it should only be used if chemical induction has failed.

Before starting treatment the patient must undergo strict clinical and laboratory examinations, and must be checked carefully during the course of treatment.

Gonadotrophins can be used for the following conditions : -

1. A patient with hypophysectomy
2. A patient with Sheehan's Syndrome
3. A patient with normal, non-functioning ovaries
4. A patient with primary amenorrhoea
5. A patient who has had amenorrhoea for a long time
6. A patient with Pituitary failure.

The side-effects are : -

1. Multiple Pregnancy
2. Hyperstimulation syndrome, which manifests itself in the enlargement of the ovaries, ovarian cysts formation, nausea, vomiting and diarrhoea, abdominal and pleural fluid formation, blood volume and coagulating changes.

Dosage:

The therapeutic dosage differs from patient to patient according to their personal response. With all the patients, the dosage has to be controlled by either, examination of a vaginal smear and cervical mucosa or by continuous assay of urinary Oestrogen. Both methods can be used together.

The treatment has to be started with HPG or HMG to produce follicular maturation, followed by HCG to produce ovulation.

- I) The dosage of HPG / HMG used is between 75 - 400 IU/day for 8 - 10 days, intramuscularly.
- II) The dosage of HCG is between 2,000 - 20,000 IU given 1 or 2 days after the last injection of HPG or HMG and then 500 - 1,500 IU every 3 to 4 days to maintain the luteal function.
In the absence of Pregnancy or ovarian enlargement, treatment is recommenced 5 days after the menstrual bleeding.

TREATMENT WITH HYPOTHALAMIC HORMONES RELEASING FACTORS

In cases of hypothalamic inhibitions and when the pituitary is in good nature ovulation can be induced by giving FSH/LH - RF either intramuscular or intravenously.

TREATMENT WITH BROMOCRIPTINE

In cases of high level of prolactin in the blood Bromocriptine can be given to antagonise the prolactin and decrease its level to normal, then to produce ovulation.

IN THE CENTRE OF STERILITY TREATMENT
(UNIVERSITY DEPARTMENT OF GYNAECOLOGY
AND OBSTETRICS - GENEVA)

The studies showed these figures :

These studies were composed of 2 groups, one group of patients, the sterility condition had been cured by Clomiphene alone and the second group had been cured by Clomiphene and HCG. A 23 cases had been chosen and treated by Clomiphene alone, which result to pregnancy, those cases had been chosen in order to study the characteristics of a better treatment in the future, and the clinical diagnoses of the above cases classified as :

8 secondary amenorrhoea, 11 primary or secondary spaniomenorrhoea with insufficient luteale phase and 2 Isomenorrhoea with latent ovulation. The 23 pregnancies induced by Clomiphene only had ended with 23 spontaneous labor. It had been observed in some cases that pregnancy had occurred:

3 times during the first cycle of treatment, 8 times during the second cycle, and 3 times during the third cycle, but at 7 times also, the pregnancy had occurred immediately after the stoppage of treatment within one or several successive months, and one case, after the second or the third cycle. Some cases did not response to the treatment by Clomiphene alone, but after treating them with Clomiphene plus HCG for induction of ovulation in the cases of luteale phase insufficiency when the Clomiphene alone had felt.

Next time 21 cases had been specifically chosen for the treatment with Clomiphene plus HCG, result pregnancy. The clinical classification of this second group composed of :

8 secondary amenorrhoea, 9 primary or secondary spaniomenorrhoea, 1 polymenorrhoea and 3 Isomenorrhoea with latent ovulation, these 21 patients had been treated by Clomiphene and HCG result 21 pregnancy during which 19 labor and 2 miscarriage had occurred.

For the indication of treatment by HCG alone, either in cases of isomenorrhoea with luteal insufficiency, or in cases of spaniomenorrhoea luteal or aluteal. Here 35 cases have been chosen where the treatment ends by pregnancy, and this has been done in order to study the characteristics of our treatment for a better and more serious future of the indications and methods of treatment. The classification of these 35 cases are : -

10 cases of primary or secondary spaniomenorrhoea, 2 cases of anisomenorrhoea, and 23 cases of isomenorrhoea with luteal insufficiency, scattered ovulation or, cycles appearing normal but with out ovulation.

The sterility has been a primary one in 21 cases and secondary in 14 cases. The average of the duration of sterility was 40 months and the average of the age was 29 years. The 35 pregenancies occurred, 10 times was during the first cycle of treatment, 6 times during the other successive 4 cycles, and 14 times during the first cycle without treatment after the stoppage of the treatment. 16 patients became pregenant during the treatment, and 19 patients became pregenant immediately after the stoppage of treatment or during the successive months after. We got 33 normal birthes of the 35 pregenancies, one cromosomal misscarriage and one extra utrine pregenancy in a patient has been operated for tubal plasty.

CLOMIPHENE

EFFECT OF TREATMENT

BEFORE TREATMENT		AFTER TREATMENT	
Oestrogens (mcg/24 h.)	Pregnandiol (mg/24 h.)	Oestrogens (mcg/24 h.)	Pregnandiol (mg/24 h.)
	<u>insufficiency</u> 12/16		
average 38.2	average 0.9	average 62.3	average 6.1
	<u>normal</u> 4/16		
	average 4.6		
(n=17/23)	(n=16/23)	(n= 17/23)	(n= 5/23)

Fig. No. 10

CLOMIPHENE + HCG

EFFECT OF TREATMENT

BEFORE TREATMENT		AFTER TREATMENT	
Oestrogens (mcg/24 h.)	Pregnandiol (mg/24 h.)	Oestrogens (mg/24 h.)	Pregnandiol (mg/24 h.)
	<u>insufficiency</u> 13/14		
average 25.6	average 1.6	average 84.1	average 8.5
	<u>normal</u> 1/14		
	average 4.0		
(n= 16/22)	(n= 14/22)	(n= 16/22)	(n= 15/22)

Fig. No. 11

HCG

EFFECT OF TREATMENT

BEFORE TREATMENT		AFTER TREATMENT	
Oestrogens (mcg/24 h.)	Pregnandiol (mg/24 h.)	Oestrogens (mcg/24 h.)	Pregnandiol (mg/24 h.)
	<u>insufficiency</u> 19/32		
average 36.5	average 1,83	average 66.8	average 6.3
	<u>normal</u> 13/32		
	average 4.7		
(n= 30/35)	(n= 32/35)	(n= 27/35)	(n= 30/35)

Fig. No. 12

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